IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: El-Naggar *et al.* Examiner: Kwon, Brian Yong S.

Serial No.: 09/943,048 Group Art Unit: 1614

Filing Date: 08/30/2001 Docket No. MOUS-4125

Title: **TREATMENT OF INFLAMMATORY, CANCER, AND THROMBOSIS DISORDERS**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

BRIEF OF APPELLANT

This Appeal Brief, pursuant to the Notice of Appeal filed June 1, 2006, is an appeal from the rejection of the Examiner in the Office Action dated March 1, 2006, in consideration of the Notice of Non-Compliant Appeal Brief mailed August 15, 2006..

REAL PARTY IN INTEREST

Mawaheb M. El-Naggar and Ahmed S. Mousa.

RELATED APPEALS AND INTERFERENCES

None.

STATUS OF CLAIMS

Claims 10-13, 15, and 18-24 are rejected. Claims 1-9, 14, and 16-17 are canceled. The

rejection of claims 10-13, 15 and 18-24 is being appealed.

STATUS OF AMENDMENTS

There are no After-Final Amendments which have not been entered. In a telephonic interview held on 07/19/2006 between the Examiner and Applicants' representative, the Examiner agreed to hold the objection to new matter under 35 USC 132 in abeyance pending outcome of the present appeal.

SUMMARY OF CLAIMED SUBJECT MATTER

A. CLAIM 10 - INDEPENDENT

A method of treating inflammatory disorders in a mammal. The method comprises concurrently administering to said mammal a therapeutic composition. The therapeutic composition comprises: (i) a standard therapeutic dose of a COX2 inhibitor selected from the group consisting of celecoxib and rofecoxib; (ii) low dose aspirin in an amount of 70-85 mg; and (iii) an antioxidant selected from the group consisting of a flavanoid, a flavonoid, an isoflavone, and combinations thereof. See specification, page 3, line 21 - page 4, line 5; page 5, lines 9-11; page 8, lines 25-29.

B. CLAIM 18 - INDEPENDENT

A pharmaceutical composition, comprising a therapeutic composition for treating inflammatory disorders in a mammal. The therapeutic composition comprises: (i) a standard

therapeutic dose of a COX2 inhibitor selected from the group consisting of celecoxib and rofecoxib; (ii) low dose aspirin in an amount of 70-85 mg; and (iii) an antioxidant selected from the group consisting of a flavanoid, a flavonoid, an isoflavone, and combinations thereof. See specification, page 3, line 21 - page 4, line 5; page 5, lines 9-11; page 8, lines 25-29.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Claims 23-24 stand rejected under 35 U.S.C. stand rejected under § 112, first paragraph, as allegedly failing to comply with the written description requirement.

2. Claim 15 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3. Claims 10-13, 18-21 and 23-24 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hedden *et al.* (WO 01/45705) in view of Langhoff (DE 19855426 A1) and Shapiro (US 6,444,221).

4. Claims 15 and 22 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hedden *et al.* (WO 01/45705) in view of Langhoff (DE 19855426 A1) and Shapiro (US 6,444,221), and further in view of Burch *et al.* (US 6,552,031) and Drug Facts and Comparison (1995 Edition, pp. 1248) and Hendeler (US 6,541,613B2).

ARGUMENT

GROUND OF REJECTION 1

Claims 23-24 under 35 U.S.C. stand rejected under § 112, first paragraph, as allegedly failing to comply with the written description requirement.

The Examiner argues: "The claims in this application introduce negative limitation as discussed in preceding comments; namely "the low dose aspirin is not covalently attached to the COX2 inhibitor". The examiner determines that when all evidences in the original disclosure are considered and carefully reviewed, the newly added claims fail to find support in the original specification.... There is no express statement about the negative limitation that can be found in the specification. Thus, the exclusion of said elements implies the inclusion of all other elements not expressly excluded, clearly illustrating that such negative limitations do, in fact, introduce new matter. The negative limitation recited in the present claims, which did not appear in the specification filed, introduces new concepts and violate the description requirement of the first paragraph of 35 USC 112."

In response, Appellants assert that matter inherently disclosed in the specification, even if not explicitly disclosed, is not new matter. See MPEP 2163.07(a) ("By disclosing in a patent application a device that **inherently** performs a function or has a property, operates according to a theory or has an advantage, a patent application necessarily discloses that function, theory or advantage, **even though it says nothing explicit concerning it**") (emphasis added)).

Appellants assert that the limitation in claims 23-24 of "wherein the low dose aspirin is not covalently attached to the COX2 inhibitor" is inherently disclosed in Appellants'

specification, so that the preceding limitation of claims 23-24 is not new matter and thus not in violation of 35 U.S.C. § 112, first paragraph.

Covalent attachment is a form of chemical binding. Therefore, in order for the low dose aspirin to be covalently attached to the COX2 inhibitor, the low dose aspirin must necessarily be chemically attached to the COX2 inhibitor by the covalent attachment. However, Par. [0024] of Appellants' specification recites: "The combined compounds of this invention may be formulated such that, although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized." Appellants assert that it is impossible for the low dose aspirin to both be chemically attached to the COX2 inhibitor and also have minimal physical contact with the COX2 inhibitor. Therefore, the preceding citation in Par. [0024] of Appellants' specification inherently discloses the low dose aspirin to not be chemically attached to the COX2 inhibitor and thus not be covalently attached to the COX2 inhibitor.

Par. [0024] of Appellants' specification further recites: "Still another approach would involve the formulation of combined compounds in which the one compound is coated with a sustained and/or enteric release polymer, and the other compound is also coated with a polymer such as a low viscosity grade of hydroxypropyl methylcellulose or other appropriate materials as known in the art, in order to further separate the active components. **The polymer coating serves to form an additional barrier to interaction with the other component**." (emphasis added). In the preceding embodiment of the present invention described in Par. [0024], the active ingredients are physically isolated from each other and prevented from interacting with each other, by the polymer coating, so that the active ingredients are not in covalent contact with each

other. Therefore, the preceding citation in Par. [0024] of Appellants' specification inherently discloses the low dose aspirin to not be covalently attached to the COX2 inhibitor.

Based on the preceding arguments, Appellants respectfully request that the rejection of claims 23-24 under 35 U.S.C. § 112, first paragraph is improper.

GROUND OF REJECTION 2

Claim 15 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner argues: "Dependent claim 11 further limits the subject matter of a previous claim 14 which was canceled. Thus, Claim 11 is vague and unclear and leaves the reader in doubt as to the meaning of the invention to which they refer, thereby rendering the definition of the subject-matter of said claims unclear.... For the examination purpose, claim 15 is understood as being dependent on the independent claim 10.... Claim 15 recites that the therapeutic composition prepared in "an enteric coated formulation". It appears in view of the independent claim 10 that each of active ingredients of the invention is administered concurrently to the patient. In other words, said therapeutic composition is not formulated together in a single dosage unit. Since the claimed "enteric coated formulation" can be formulated when the composition is prepared in a single dosage unit, the applicant's failure to further limit the subject matter of the previous claim leaves the reader in doubt as to the meaning of the invention to which they refer, thereby rendering the definition of the subject-matter of said claims unclear."

In response, Appellants note that the Examiner has entered Appellants' amendment of claim 15 such that the amended claim in the present appeal depends from claim 10 and not from claim 14.

As to the Examiner's allegation that claim 15 fails to further limit claim 10, Appellants argue that the recited ingredients of claim 10 could be administered concurrently in ways other

than through use of an enteric coated formulation. As described in Par. [0028] of the present patent application, "the compounds may be formulated together, in a single dosage unit (that is, combined together in one capsule, tablet, powder, or liquid, etc.) as a combination product". Therefore, requiring the composition to be in an enteric coated formulation in claim 15, which is not recited in claim 10, further limits claim 10.

Based on the preceding arguments, Appellants respectfully request that the rejection of claim 15 under 35 U.S.C. § 112, second paragraph is improper.

GROUND OF REJECTION 3

Claims 10-13, 18-21 and 23-24 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hedden *et al.* (WO 01/45705) in view of Langhoff (DE 19855426 A1) and Shapiro (US 6,444,221).

Appellants respectfully contend that claims 10 and 18 are not unpatentable over Hedden in view of Langhoff and Shapiro, because Hedden in view of Langhoff and Shapiro does not teach or suggest each and every feature of claims 10 and 18.

A first reason why claims 10 and 18 are not unpatentable over Hedden in view of Langhoff and Shapiro is that Hedden in view of Langhoff and Shapiro does not teach or suggest the feature: "low dose aspirin in the amount of 70-85 mg".

The Examiner argues: "Langhoff teaches the use of low dose aspirin(in dosage range of 30mg-75mg) for the treatment of anti-inflammatory disorder including rheumatism and arthritis.... It is obvious to combine two compositions each of which is taught by prior art to be useful for same purpose; idea of combining them flows logically from their having been individually taught in the prior art. The combination of active ingredient with the same character is merely the additive effect of each individual component. *See In re Kerkhoven, 205 USPQ 1069 (CCPA 1980).*"

In the Advisory Action mailed 05/26/2006, the Examiner additionally argues: "Langhoff clearly teaches the use of low dose aspirin is doses 30mg-75mg, preferably 35-40 mg for the treatment of rheumatism and arthritis. (See abstract; page 2, lines 32-34 and 57-68, claims 14-19, particularly claim 19). Thus, the skilled artisan would be able to arrive at the claimed invention vin combination with the cited references."

In response in consideration of the fact that Langhoff appears published in the German language, Appellants present in Tables 1 and 2 below, to the best of Appellants' ability, an English translation of the specific portions of Langhoff cited by the Examiner.

Table 1. Citations to Langhoff (page 1 (57) abstract; page 2, lines 32-35; page 2, lines 57-68)

Cite in Langhoff	Text of Citation
Page 1 (57) Abstract	The invention is a pharmaceutical compound, containing at least a ω-3-unsaturated fatty acid and/or its physiologically compatible derivatives, vitamin E, vitamin C, and acetylsalicylic acid. This compound is used for the treatment of rheumatic-arthritic diseases and to prevent cardiovascular diseases in humans and animals.
Page 2, lines 32-35	It was one task of the invention to provide a pharmaceutical compound that is an improvement for the treatment and prevention of inflammation processes in the body, particularly for treating and preventing rheumatic-arthritic problems as well as preventing cardio-vascular problems.
Page 2, lines 57-68	For the invention, the acetylsalicylic acid is used in very minute amounts: less than 75 mg/day, preferably less than 60 mg/day, so the effect of hindering *thrombozyten* aggregation was not observed. The known side effects of acetylsalicylic acid, such as stomach bleeding or pseudo-allergic reactions, did not occur. No known substance can attain the same effect of hindering inflammation of rheumatic-arthritic and cardio-vascular diseases with such minimal side effects as does this invention compound. The compound is intended for oral dispensing and can be considered in various different forms: powder, tablet, pill, capsule, solution, concentrate, syrup, suspension, gel, or in the form of a dispersion. The compound can be prescribed so that the total amount of acetylsalicylic acid available to the body is between 30 and 75 mg per day, preferably between 35 and 45 mg per day (for a person with a body weight of approximately 75 kg). The appropriate quantity…

Table 2. Citation to Langhoff (Claims 1 and 14-19)

Cite in Langhoff	Text of Citation
Claims 1, 14-19	1. Pharmaceutical compound encompassing (a) at least a ω-3-unsaturated fatty acid and/ or its physiologically compatible derivative (b) vitamin E, (c) vitamin C, and (d) acetylsalicylic acid. 14. Remedy according to claim 13 for the treatment and prevention of rheumatic-arthritic diseases as well as prevention of cardio-vascular diseases. 15. Remedy according to claim 14 for the treatment and prevention of rheumatism and arthritis and for the prevention of heart attack, arteriosclerosis, *stenos*, and thrombosis. 16. Use of the compound as defined in any of the claims 1 through 12 for the treatment of inflammation diseases in humans or in animals. 17. Use according to claim 16 for the treatment and prevention of rheumatic-arthritic diseases and/or prevention of cardio-vascular diseases. 18. Use according to claim 17 for the treatment and prevention of rheumatism and arthritis and prevention of heart attack, arteriosclerosis, *stenoe*, and thrombosis. 19. Use according to any of the claims 16 through 18 in a dose of 30 to 75 mg of acetylsalicylic acid per day.

Appellants acknowledge that Langhoff teaches the use of pharmaceutical compound encompassing a ω-3-unsaturated fatty acid, vitamin E, vitamin C, and vitamin C, and

acetylsalicylic acid (i.e., aspirin) in a dosage range of 30 mg-75 mg, for the treatment of rheumatic-arthritic diseases and for the prevention of cardiovascular diseases.

However, none of the citations to Langhoff in Tables 1 and 2 teach or suggest that aspirin (i.e.,acetylsalicylic acid) having a dosage not exceeding 75 mg contributes to the treatment of rheumatic-arthritic diseases outside of Langhoff's disclosed composition.

In addition, none of the citations to Langhoff in Tables 1 and 2 teach or suggest that aspirin having a dosage not exceeding 75 mg contributes, by itself, to the treatment of rheumatic-arthritic diseases.

Moreover, none of the citations to Langhoff in Tables 1 and 2 teach or suggest that Langhoff's pharmaceutical compound would be less effective in treating rheumatic-arthritic diseases if the aspirin were removed from the pharmaceutical compound.

Next, Appellants present next an English translation of the example on page 5 of Langhoff, which indicates that aspirin having a dosage not exceeding 80 mg does not contribute to the treatment of rheumatic-arthritic diseases.

CITATION TO EXAMPLE IN PAGE 5 OF LANGHOFF

For the following example cod liver oil, vitamin E, vitamin C and acetylsalicylic acid are used in pure forms. An experiment using flax oil for the source of the ω-3-unsaturated fatty acid (α linoleic acid) produced the same results.

The inflammation hindering effect of the following formulation is compared for a person (body weight around 75 kg), who suffers primarily from rheumatic-arthritic diseases as well as from a mild cardio-vascular disease.

A) 10 g cod liver oil, 1000 mg vitamin E, 1000 mg vitamin C

B) 80 mg acetylsalicylic acid

C) 250 mg vitamin E, 40 mg acetylsalicylic acid

D) 50% of A) and 50% of B)

The dispensing of the above named amounts took place daily, in individual doses, over a period of fourteen weeks. Using a value system (1= very good; 2=good; 3=satisfactory; 4= sufficient; 5=barely noticeable alleviation; 6=no alleviation), the test subject described the results thus:

compound	evaluation
A	2
B	6
C	3
D	1

END OF CITATION TO EXAMPLE IN PAGE 5 OF LANGHOFF

Appellants conclude from the preceding example on page 5 of Langhoff as follows:

(1) The evaluation of "6" for compound B) indicates that 80 mg acetylsalicylic acid is not effective in treating rheumatic-arthritic diseases;

(2) An evaluation of "3" for compound C), in comparison with the evaluation of "6" for compound B), indicates that the "satisfactory" alleviation of the rheumatic-arthritic diseases is due to the 250 mg vitamin E and not to the acetylsalicylic acid; and

(2) An evaluation of "1" for compound D), in comparison with the evaluation of "6" for compound B), indicates that the "very good" alleviation of the rheumatic-arthritic diseases is due to the (10 g cod liver oil, 1000 mg vitamin E, 1000 mg vitamin C) and not to the acetylsalicylic acid.

Based on the preceding analysis of Langhoff, Appellants contend that Langhoff's data does not support the use of aspirin in a dosage range of 30-75 mg to treat inflammatory disorders in a mammal.

Appellants respectfully contend that it is known in the art that low dose aspirin in doses of 30-75 mg is not effective in the treatment of inflammatory disorder, as evidenced by numerous published papers. Appellants next cite the abstract of several articles to illustrate that much higher doses of aspirin that 30-75 mg are required for therapeutically effective treatment of inflammatory disorder.

See Calin A. "Pain and inflammation", Am J Med. 1984 Sep 10;77(3A):9-16. The abstract of the preceding reference (Calin) is as follows:

> "The traditional "aspirin first" approach to the treatment of osteoarthritis and rheumatoid arthritis is undergoing serious reappraisal. Aspirin and acetaminophen are equipotent in their analgesic efficacy; however, aspirin is associated with a higher incidence of side effects. Acetaminophen should therefore be used as first-line therapy for the treatment of osteoarthritis since reduction of pain is the primary therapeutic objective. Analgesic doses of aspirin (up to 3,900 mg per day) do not produce an anti-inflammatory effect and thus are not beneficial in the treatment of rheumatoid arthritis. **Only high doses of aspirin (4 to 6 g per day) used for a sustained period produce an anti-inflammatory effect.** Since many patients with rheumatoid arthritis cannot tolerate long-term use of anti-inflammatory doses of aspirin, it may be preferable to initiate therapy with one of the newer nonsteroidal anti-inflammatory drugs."

See, Gomes I, "Aspirin: a neuroprotective agent at high doses?", Natl Med J India. 1998 Jan-Feb;11(1):14-7. The abstract of the preceding reference (Gomes) is as follows:

> "Aspirin, acetylsalicylic acid, is routinely used in clinics as an analgesic, antipyretic and in the secondary prevention of stroke. These effects are caused by low doses of the drug (0.3-3.6 g/day) through the inhibition of cyclo-oxygenase, the enzyme responsible for prostaglandin synthesis. **Higher doses of aspirin (4-6 g/day) are used in the treatment of inflammatory conditions such as rheumatoid arthritis** and recent laboratory findings suggest that it could play a role in neuroprotection against glutamate excitotoxicity. This article reviews the possible mechanisms of action of high-dose aspirin in neuroprotection."

See Appelrouth DJ, Baim S, Chang RW, Cohen MH, Englund DW, Germain BF, Hartman SS, Jaffer A, Mullen BJ, Smith FE, "Comparison of the safety and efficacy of nabumetone and aspirin in the treatment of osteoarthritis in adults", Am J Med. 1987 Oct 30;83(4B):78-81. The abstract of the preceding reference (Appelrouth et al.) is as follows:

> A six-month, multicenter, double-blind study compared the efficacy and safety of two therapeutic regimens in 332 patients with osteoarthritis. The patients received either 1,000 mg of nabumetone as a single bedtime dose or **900 mg of aspirin in four divided doses**. At the end of the study, patients in both treatment groups showed significant improvement from baseline for all five parameters; no statistically or clinically significant differences were observed between the groups. The safety data did reveal clinically and statistically significant differences between the groups. Aspirin-treated patients experienced a greater frequency of withdrawal from the study because of adverse experiences (34 percent versus 13 percent), a greater incidence of having at least one treatment-related adverse experience (73 percent versus 52 percent), a greater percentage of patients with at least one moderate or severe treatment-related adverse experience (47 percent versus 22 percent), and a greater percentage of patients with treatment-related adverse experiences affecting the gastrointestinal system (43 percent versus 32 percent) or the inner ear (32 percent versus 10 percent). The results of this study demonstrated that nabumetone, 1,000 mg at bedtime, is as efficacious as **aspirin, 900 mg four times daily**, produces fewer adverse effects, and is indicated in the treatment of osteoarthritis.

See Fries JF, Ramey DR, Singh G, Morfeld D, Bloch DA, Raynauld JP, "A reevaluation of aspirin therapy in rheumatoid arthritis", Arch Intern Med. 1993 Nov 8;153(21):2465-2471. The abstract of the preceding reference (Fries et al.) is as follows:

> "Aspirin therapy has been largely superseded by prescription nonsteroidal anti-inflammatory drug (NSAID) therapy in rheumatoid arthritis, in part because of premarketing studies suggesting lesser toxic effects for NSAIDs than for aspirin. This study evaluates these toxic effects in a postmarketing population of patients with rheumatoid arthritis. METHODS: We studied 1521 consecutive courses of aspirin and 4860 courses of NSAIDs in patients with rheumatoid arthritis from eight Arthritis, Rheumatism, and Aging Medical Information System Post-marketing Surveillance Centers. Toxicity index scores were generated from symptoms, laboratory abnormalities, and hospitalizations, weighted for variable severity and severity of side effect. RESULTS: The toxicity index was only 1.37 (SE = 0.10) for aspirin and 1.87 to 2.90 for selected nonsalicylate NSAIDs. These differences were consistent across centers and remained after statistical adjustment for differing patient characteristics. There was a different toxicity with different aspirin preparations, with a score for plain aspirin of 1.36 (SE = 0.23), for buffered aspirin of 1.10 (0.20), and for enteric-coated aspirin preparations of 0.92 (0.14). Most important, there were strong dose effects, with a score of 0.73 (0.09) for **651 to 2600 mg daily**, 1.08 (0.17) for 2601 to 3900 mg, and 1.91 (0.38) for **more than 3900 mg**. The average aspirin dose taken was only 2665 mg/d, approximately eight "tablets," compared **with 3600 to 4800 mg/d** used in the 16 pivotal premarketing studies reviewed. Average NSAID doses were, on the other hand, lower in premarketing trials (eg, naproxen 500 mg/d vs 773 mg/d in the Arthritis, Rheumatism, and Aging Medical System clinical practices). CONCLUSIONS: Aspirin therapy, in doses commonly employed in practice, has an excellent safety profile in rheumatoid arthritis, and it is the least costly NSAID.

The safety advantage is explained primarily by a dose effect and secondarily by possible differences between formulations. Newer management strategies for rheumatoid arthritis emphasize NSAID use as symptomatic therapy and use of disease-modifying anti-rheumatic drug therapy for anti-inflammatory objectives. Thus, the original recommendation for "anti-inflammatory" doses of aspirin now is less easily justified. Aspirin therapy merits reconsideration as adjunctive therapy for the management of rheumatoid arthritis."

See Edwards, W., "Etodolac, aspirin, and placebo in patients with rheumatoid arthritis: a 12-week study", Clin Ther. 1983;5(5):495-503. The abstract of the preceding reference (Edwards) is as follows:

"Etodolac, aspirin, and placebo were evaluated for efficacy and safety in 18 patients with adult-onset, active rheumatoid arthritis. This was a 12-week, double-blind, parallel-group study divided into drug titration and maintenance periods and preceded by a washout period of up to two weeks. The mean daily maintenance doses of etodolac and aspirin were **394 mg and 4,414 mg**, respectively. Etodolac was significantly (P less than or equal to 0.05) more effective than placebo in five of ten clinical variables of efficacy: number of painful joints, number of swollen joints, pain intensity, erythrocyte sedimentation rate, and patients' overall assessments. Aspirin was significantly more effective than placebo in only two assessments: number of painful joints and pain intensity. One patient on etodolac, two patients on aspirin, and four patients on placebo had to be withdrawn from the trial because of insufficient therapeutic response. One patient in the placebo group was withdrawn from the study because of a pruritic rash. Mild to moderate gastrointestinal complaints occurred in all three treatment groups: in three patients taking etodolac, three taking aspirin, and two taking placebo."

See Kolarz G., "Double-blind, cross-over, international multicentre investigation of two doses of indoprofen compared with ASA and placebo in rheumatoid arthritis", Eur J Rheumatol Inflamm., 1981;4(1):53-59. The abstract of the preceding reference (Kolarz) is as follows:

> "Indoprofen **600 mg or 1000 mg/day, ASA 3600 mg/day** and placebo were administered in randomized sequences according to a multiple 4 x 4 latin square design, balancing the treatments, periods and residual effects. Each treatment lasted 7 days. A total of 98 patients suffering from classical or definite rheumatoid arthritis completed the study. Analysis of the effectiveness indicates that both doses of indoprofen and ASA are significantly more active than placebo; indoprofen 1000 mg/day was the treatment preferred in most of the cases. Both doses of indoprofen were better tolerated than ASA."

In summary, the preceding evidence demonstrates that aspirin doses of 394 mg to 6,000 mg are therapeutically effective in the treatment of inflammatory disorder. The Examiner has not provided any credible scientific evidence allegedly demonstrating that low dose aspirin in doses of 30-75 mg is therapeutically effective in the treatment of inflammatory disorders. Accordingly, Appellants contend that it is not obvious to modify Hedden to add aspirin in the amount of 70-85 mg to a standard therapeutic dose of COX2 inhibitor for the treatment of inflammatory disorder.

Appellants contend that it is additionally not obvious to modify Hedden to add aspirin in the amount of 70-85 mg to a standard therapeutic dose of COX2 inhibitor (i.e., of celecoxib or rofecoxib), because the Examiner has not cited any evidence from the prior art suggesting that the effectiveness of COX2 inhibitor in treating inflammatory disorders would be enhanced by the addition of aspirin in the amount of 70-85 mg.

A second reason why claims 10 and 18 are not unpatentable over Hedden in view of Langhoff and Shapiro is that Hedden in view of Langhoff and Shapiro does not teach or suggest the feature: "an antioxidant selected from the group consisting of a flavanoid, a flavonoid, an isoflavone, and combinations thereof".

The Examiner argues: "Shapiro (US 6444221) teaches the use of flavonoids, flavanoids and isoflavones (i.e., daidzin, genistein, quercetin, silymarin, etc...) as antioxidants having functional equivalent property for the treatment of inflammatory disease conditions (column 9, line 52 thru column 19, line 32; column 20, line 47 thru column 21, line 8)."

In response, Appellants contend that Shapiro teaches that the disclosed flavonoids, flavanoids and isoflavones as antioxidants are useful in treating of inflammatory disease only in combination with carbonyl trapping agents. See Shapiro, col, 10, lines 43-51. See also, Shapiro, col, 10, lines 59-67 ("In another preferred embodiment, use of a primary agent in combination with a clinically effective anti-oxidant and lipid peroxidation inhibitor co-agent may be of particular benefit in preventing or ameliorating forms of chronic inflammation by incorporating two pharmacological strategies, the sequestering of cytotoxic aldehydes and ketones generated at sites of chronic inflammation and the sequestering of activated oxygen chemical species generated earlier in the non-enzymatic inflammatory cascade."). In Shapiro's composition, the carbonyl trapping agent is the primary ingredient and the antioxidant in one of several alternative secondary ingredients. Shapiro does not teach that the antioxidant by itself is therapeutically effective in treating inflammatory disease.

Therefore, Appellants respectfully contend that Shapiro does not teach that the disclosed

flavonoids, flavanoids and isoflavones as antioxidants are useful in treating of inflammatory disease in combination with low dose aspirin and COX2 inhibitor, since aspirin and COX2 inhibitor are not carbonyl trapping agents. Accordingly, it would not be obvious to add the disclosed flavonoids, flavanoids and isoflavones as antioxidants to a composition of aspirin and COX2 inhibitor for the purpose of treating of inflammatory disease.

Based on the preceding arguments, Appellants respectfully maintain that claims 10 and 18 are not unpatentable over Hedden in view of Langhoff and Shapiro, and that claims 10 and 18 are in condition for allowance. Since claims 11-13 and 24 depend from claim 10, Appellants contend that claims 11-13 and 24 are likewise in condition for allowance. Since claims 19-21 and 23 depend from claim 18, Appellants contend that claims 19-21 and 23 are likewise in condition for allowance.

GROUND OF REJECTION 4

Claims 15 and 22 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hedden *et al.* (WO 01/45705) in view of Langhoff (DE 19855426 A1) and Shapiro (US 6,444,221), and further in view of Burch *et al.* (US 6,552,031) and Drug Facts and Comparison (1995 Edition, pp. 1248) and Hendeler (US 6,541,613B2).

The Examiner rejected claims 15 and 22 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hedden *et al.* (WO 01/45705) in view of Langhoff (DE 19855426 A1) and Shapiro (US 6,444,221), and further in view of Burch *et al.* (US 6,552,031) and Drug Facts and Comparison (1995 Edition, pp. 1248) and Hendeler (US 6,541,613B2).

Since claims 15 and 22 respectively depend from claims 10 and 18, which Appellants have argued *supra* to not be unpatentable over Hedden in view of Langhoff and Shapiro under 35 U.S.C. §103(a), Appellants maintain that claims 15 and 22 are likewise not unpatentable over Hedden in view of Langhoff and Shapiro Jones in view of Smith and further in view of Burch, Drug Facts and Comparison, and Hendeler under 35 U.S.C. §103(a).

SUMMARY

In summary, Appellant respectfully requests reversal of the March 1, 2006 Office Action rejection of claims 10-13, 15 and 18-24.

Respectfully submitted,

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Applicant: El-Naggar *et al.* Examiner: Kwon, Brian Yong S.

Serial No.: 09/943,048 Group Art Unit: 1614

Filing Date: 08/30/2001 Docket No. MOUS-4125

Title: **TREATMENT OF INFLAMMATORY, CANCER, AND THROMBOSIS DISORDERS**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPENDIX A - CLAIMS ON APPEAL

10. A method of treating inflammatory disorders in a mammal, said method comprising concurrently administering to said mammal a therapeutic composition, said therapeutic composition comprising: (i) a standard therapeutic dose of a COX2 inhibitor selected from the group consisting of celecoxib and rofecoxib; (ii) low dose aspirin in an amount of 70-85 mg; and (iii) an antioxidant selected from the group consisting of a flavanoid, a flavonoid, an isoflavone, and combinations thereof.

11. The method of claim 10, wherein the antioxidant comprises the flavanoid.

12. The method of claim 10, wherein the antioxidant comprises the flavonoid.

13. The method of claim 10, wherein the antioxidant comprises the isoflavone.

15. The method of claim 10, wherein the therapeutic composition is in an enteric coated formulation.

18. A pharmaceutical composition, comprising a therapeutic composition for treating inflammatory disorders in a mammal, said therapeutic composition comprising: (i) a standard therapeutic dose of a COX2 inhibitor selected from the group consisting of celecoxib and rofecoxib; (ii) low dose aspirin in an amount of 70-85 mg; and (iii) an antioxidant selected from the group consisting of a flavanoid, a flavonoid, an isoflavone, and combinations thereof.

19. The pharmaceutical composition of claim 18, wherein the antioxidant comprises the flavanoid.

20. The pharmaceutical composition of claim 18, wherein the antioxidant comprises the flavonoid.

21. The pharmaceutical composition of claim 18, wherein the antioxidant comprises the isoflavone.

22. The pharmaceutical composition of claim 18, wherein the therapeutic composition is in an enteric coated formulation.

23. The pharmaceutical composition of claim 18, wherein the low dose aspirin is not covalently attached to the COX2 inhibitor.

24. The method of claim 10, wherein the low dose aspirin is not covalently attached to the COX2 inhibitor.

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APPENDIX B - EVIDENCE

There is no evidence entered by the Examiner and relied upon by Appellant in this appeal.

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Filing Date: 08/30/2001 Docket No. MOUS-4125

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Commissioner for Patents
P.O. Box 1450
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APPENDIX C - RELATED PROCEEDINGS

There are no proceedings identified in the "Related Appeals and Interferences" section.